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Inequality in survival of people with head and neck cancer: Head and Neck 5000 cohort study

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Abstract

Background: Explanations for socioeconomic inequalities in survival of head and neck cancer (HNC) patients have had limited attention and are not well understood.

Methods: The UK Head and Neck 5000 prospective clinical cohort study was analyzed. Survival relating to measures of socioeconomic status was explored including area-based and individual factors. Three-year overall survival was determined using the Kaplan–Meier method. All-cause mortality was investigated via adjusted Cox Proportional Hazard models.

Results: A total of 3440 people were included. Three-year overall survival was 76.3% (95% CI 74.9, 77.7). Inequality in survival by deprivation category, highest education level, and financial concerns was explained by age, sex, health, and behavioral factors. None of the potential explanatory factors fully explained the inequality associated with annual household income or the proportion of income of benefits.

Conclusion: These results support the interventions to address the financial issues within the wider care and support provided to HNC patients.

KEYWORDS

cancer epidemiology, cohort study, head and neck cancer, inequality, Kaplan–Meier, survival

1 | INTRODUCTION

Inequality in survival of people with cancer is well documented both globally¹⁻⁵ and in the United Kingdom (UK).⁶⁻⁸ Many studies highlight that people with cancer who are from disadvantaged socioeconomic backgrounds experience worse outcomes than those from more affluent backgrounds.¹⁻⁸ Potential explanations for inequality differ between studies and remain unclear. However, explanations for inequality in survival of people with cancer are an important and unsolved issue in medical research.

Possible explanations for inequality in survival of people with head and neck cancer (HNC) include suggestions that participants who were at a socioeconomic disadvantage presented with cancers at a more advanced stage, or that they presented more frequently with additional comorbidities.^{3,9-11} However, results from other studies have reported conflicting findings.¹² Previous work from a cohort of people in Scotland suggested that inequality in survival of people with HNC can be explained by a combination of demographics, tumor and treatment factors.¹³

At present, HNC accounts for nearly 900 000 cases and more than 450 000 deaths per year throughout the world.¹⁴ There were nearly 12 000 new cases of HNC and more than 4000 deaths attributable to the disease in the UK in 2016.¹⁵ The main risk factors of HNC are smoking and alcohol consumption,^{16,17} and in recent years, the human papillomavirus (HPV) has shown to be associated with the rising incidence of oropharyngeal cancer.¹⁸ Low socioeconomic position is an additional and independent risk factor of HNC and inequality in incidence of HNC has been observed between and within developed and developing countries.¹⁹⁻²¹

Other studies have relied on either area-based or individual measures of socioeconomic status (SES) to document and explain potential explanatory factors of inequality in survival of people with cancer. No prior study has investigated both forms of measurements of SES. This study aims to undertake an in-depth exploration into the nature and extent of inequality in survival of people with HNC by considering area-based and individual dimensions of socioeconomic circumstances and, in addition, to understand the underlying cause of this inequality.

2 | MATERIALS AND METHODS

2.1 | Data collection

HN5000 is a prospective clinical cohort study of people with HNC. The study has been described in detail

elsewhere.^{22,23} Briefly, people with a new diagnosis of HNC in England, Wales and Scotland, were recruited to the study between April 5, 2011 and December 31, 2014. Information was gathered from clinical records using data capture forms which were completed by research staff on participants' diagnoses and treatment modality. In addition, participants were asked to complete three questionnaires at baseline prior to the start of treatment, at 4 months after diagnosis, and at 12 months after diagnosis. At each time point, the participants were asked about their demographics, health, behaviors and a variety of information about their socioeconomic position (described in detail later). In addition, there were also separate questionnaire sheets enquiring about the participants' outlook and feelings at each time point, and about their sexual behavior history at baseline. Full ethical approval was granted by the National Research Ethics Committee (South West Frenchay Ethics Committee, reference 10/H0107/57, November 5, 2010) and it was approved by the Research and Development departments for the participating NHS trusts.

2.2 | SES variables

2.2.1 | Area-based measurement of SES

The area-based measurement of SES was derived from English Index of Multiple Deprivation (IMD) 2010 scores²⁴ which were linked to HN5000 using the participants' home postcodes and Lower Layer Super Output Area codes.²⁵ IMD 2010 categorizes geographical areas in England using information from seven domains including: Income Deprivation; Employment Deprivation; Health Deprivation and Disability; Education Skills and Training Deprivation; Barriers to Housing and Services; Living Environment Deprivation and Crime. The IMD 2010 score has five categories—group 1 represents the most deprived areas and group 5 represents the least deprived areas.

2.2.2 | Individual measurements of SES

Individual measurements of SES were obtained from participants' questionnaire responses at baseline before treatment started. This included: highest education level attained, number of years in full-time education, total annual household income, proportion of income from benefits, and financial concerns of living with or after cancer. The highest education level that the participants had attained was grouped as: (a) up to secondary school (primary school or secondary school, usually including

students up to the age of 16), (b) further education (school/college sixth form or further education college, usually including students between the ages of 16 to 18), or (c) higher education or university (university or polytechnic university, usually including students aged 18 and over). The number of years spent in education was categorized as: (a) 10 years or less, (b) 11 to 13 years, or (c) 14 years or more, and the total annual household income of the participants was grouped as: (a) less than £11 999 a year, (b) between £12 000 (approximately 18 826 US\$ in August 2012) and £28 999 a year, or (c) more than £29 000 a year (approximately 45 497 US\$ in August 2012). Note that in the financial year 2012/2013 the median disposable income in the UK was approximately £24 200. The total proportion of a participant's income received from benefits was recorded on the questionnaire as: (a) all, (b) about three quarters, (c) about half, (d) about a quarter, (e) very little, or (f) none, but for the purpose of this analysis, this was grouped as: (a) all, (b) some (groups b to e), or (c) none. Whether the participants had any financial concerns of living with or after cancer or not was recorded as: (a) yes, or (b) no.

2.3 | Potential explanatory factors

2.3.1 | Demographic data

Participants' age at the date of consent and their sex were recorded on data capture forms. Marital status was recorded on the baseline questionnaire as: (a) single, (b) widowed, (c) separated, (d) married, (e) divorced, or (f) living with a partner, and for the purpose of this analysis, this was grouped as: (a) single; (b) married or living with a partner; or (c) separated, divorced or widowed.

2.3.2 | Health status

Health status was recorded via comorbidity and World Health Organization (WHO) Performance Status²⁶ from baseline data before treatment started. Comorbidity was recorded on the baseline data capture form using the Adult Comorbidity Evaluation (ACE-27),²⁷ which categorizes participants as having: (a) no comorbidity, (b) mild comorbidity, (c) moderate comorbidity, or (d) severe comorbidity—for the purpose of this analysis the worst two comorbidities were grouped into a “moderate/severe” category. WHO Performance Status was measured on the participants' baseline questionnaire and recorded as: (a) normal activity, (b) strenuous activity restricted, (c) up and about for more than 50% of their

waking hours, (d) confined to a bed or chair for more than 50%, or (e) confined to a bed or chair for 100% of their waking hours. Due to small numbers, the worst two WHO Performance Status categories were combined into a “confined to a bed or chair for more than 50% of their waking hours” category.

2.3.3 | Behavioral factors

Participants' behavioral data were recorded on smoking status and alcohol consumption. Smoking status was recorded on the baseline questionnaire and was defined as: (a) current smoker, (b) previous smoker, or (c) never smoked, where smoking was defined as having smoked at least one cigarette during a whole year. The number of units of alcohol per week that the participants drank was calculated from baseline questionnaire responses to: (a) how many days per week they drank alcohol; and (b) how many bottles of wine, spirits, or pints of beers/lager/cider they drank each week before they were diagnosed with cancer. Using these responses, participants' alcohol consumption was calculated in units and was subsequently grouped as: (a) none, (b) moderate (more than zero and less than 14 units per week for men and women), (c) hazardous (between 14 and 50 units per week for men, and between 14 and 35 units per week for women), or (d) harmful (more than 50 units per week for men, and more than 35 units per week for women).²⁸

2.3.4 | Tumor and treatment factors

Tumor and treatment factors included information on the anatomical site of the tumor, tumor stage, HPV status, and treatment modality. Anatomical site was determined using the International Classification of Diseases Version 10 (ICD-10).²⁹ Tumors of the lip and oral cavity (C00, C02-C06), oropharynx (C01, C05.1, 2, C09.0, 1, 9, C10.0, 2, 3), nasopharynx (C11), hypopharynx (C12, C13), larynx (C32.0, 1, 2, C10.1), nasal cavity (C30.0), sinuses (C31.0, 1), major salivary glands (C07, C08), minor salivary glands (any ICD-10 code with histology recorded as “salivary gland”), and other sites of the head and neck (C14.0, C30.1, C41.1, C69.5) were included. Due to small numbers, participants with cancers of the nasopharynx, nasal cavity, sinuses, and other sites of the head and neck were combined into one group and labeled as “Other.” Tumor stage was classified using the tumor, node and metastases (TNM) Classification of Malignant Tumors from the International Union Against Cancer (UICC), Seventh Edition, which divides tumors into four categories from stage I to stage IV.³⁰ HPV status

was determined by the German Cancer Research Center (DKFZ) in Heidelberg. An HPV-positive result was determined from a serological response to HPV16 E6 antibodies using a glutathione S-transferase multiplex assay, with a cut-off value of more than 1000 Median Fluorescence Intensity units.³¹ Participants' treatment modality was extracted from data capture forms at four-months and grouped as: (a) surgery only; (b) chemoradiotherapy only; (c) radiotherapy only; (d) surgery combined with chemotherapy, chemoradiotherapy or radiotherapy; (e) chemotherapy only; or (f) no treatment.

2.4 | Mortality linkage

On October 11, 2018, the cohort was linked to the National Office of Statistics from the UK Health and Social Care Information Centre. The number of days between the date of consent and the date of death or the most recent follow-up period were calculated.

2.5 | Exclusion criteria

Participants were excluded from the HN5000 if they: (a) had withdrawn, or (b) were found to be ineligible because a biopsy result confirmed that they did not have HNC. For this analysis, we also excluded people who had a carcinoma in situ, a cancer of stage 0, thyroid cancer, cancer of unknown primary (CUP), did not live in England (and therefore could not be linked to IMD data), and those who did not return their baseline questionnaire pack.

2.6 | Statistical analyses

All statistical analyses were performed using Stata Version 16.³² Numbers and proportions of deaths were displayed for each of the participant, demographic, health, behavioral, tumor, treatment, and SES factors. SES factors were cross-tabulated with each participant, demographic, health, behavioral, tumor, and treatment factors. Three-year survival was determined using the Kaplan–Meier method and tests for the differences between the results were determined using the log-rank test. Adjusted Cox Proportional Hazard models for all-cause mortality were displayed to identify the potential explanatory factors of the inequality in survival. Hazard ratios (HRs) with 95% confidence intervals (CIs) and *p*-values for each SES variable were produced to measure the differences in all-cause mortality. Models were adjusted by: (a) age and sex; (b) age, sex, and each individual factor separately

including comorbidity, smoking status, alcohol consumption, anatomical site, stage, HPV status, and treatment modality; (c) age, sex, and health and behavioral factors combined including comorbidity, smoking status, and alcohol consumption; (d) age, sex, tumor, and treatment factors combined including anatomical site, stage, HPV status, and treatment modality; and (e) age, sex, and all potential explanatory factors combined including comorbidity, smoking status, alcohol consumption, anatomical site, stage, HPV status, and treatment modality.

2.7 | Multiple imputation

The impact of missing data on the adjusted Cox Proportional Hazard models was explored for each potential explanatory and SES variable and multiple imputation (MI) was performed to impute values for missing data.³³ The *ICE* package for the MI of chained equations in Stata 16 was used.³⁴ Twenty imputed datasets were generated using a model which included the event indicator for death, the Nelson–Aalen estimator of the cumulative hazard,³⁵ all SES variables and all potential explanatory factors. The results of the Cox Proportional Hazard models following MI were computed using the *mim* command in Stata 16,³⁶ which combines the results from each imputed dataset using Rubin's Rules, incorporating both within and between imputation variability, based on asymptotic theory.³⁷

3 | RESULTS

3.1 | Inclusion

A total of 5511 participants were recruited to HN5000; however, 107 (1.9%) participants were excluded from the cohort due to either withdrawing, being ineligible due to not having an HNC primary, not consenting to the study, or having a tumor of stage 0 (Figure 1). In addition, a total of 1964 (36.3%) participants were excluded from this analysis due to having thyroid cancer, CUP, residing in Scotland or Wales, or not returning their baseline questionnaire pack. Thus, a total of 3440 were eligible for this analysis—62.4% of the original 5511 people that were recruited.

3.2 | Missing data

Some data were missing for several potential explanatory variables which ranged from 0.9% for tumor stage to 15.0% for total annual household income (Tables 1 and

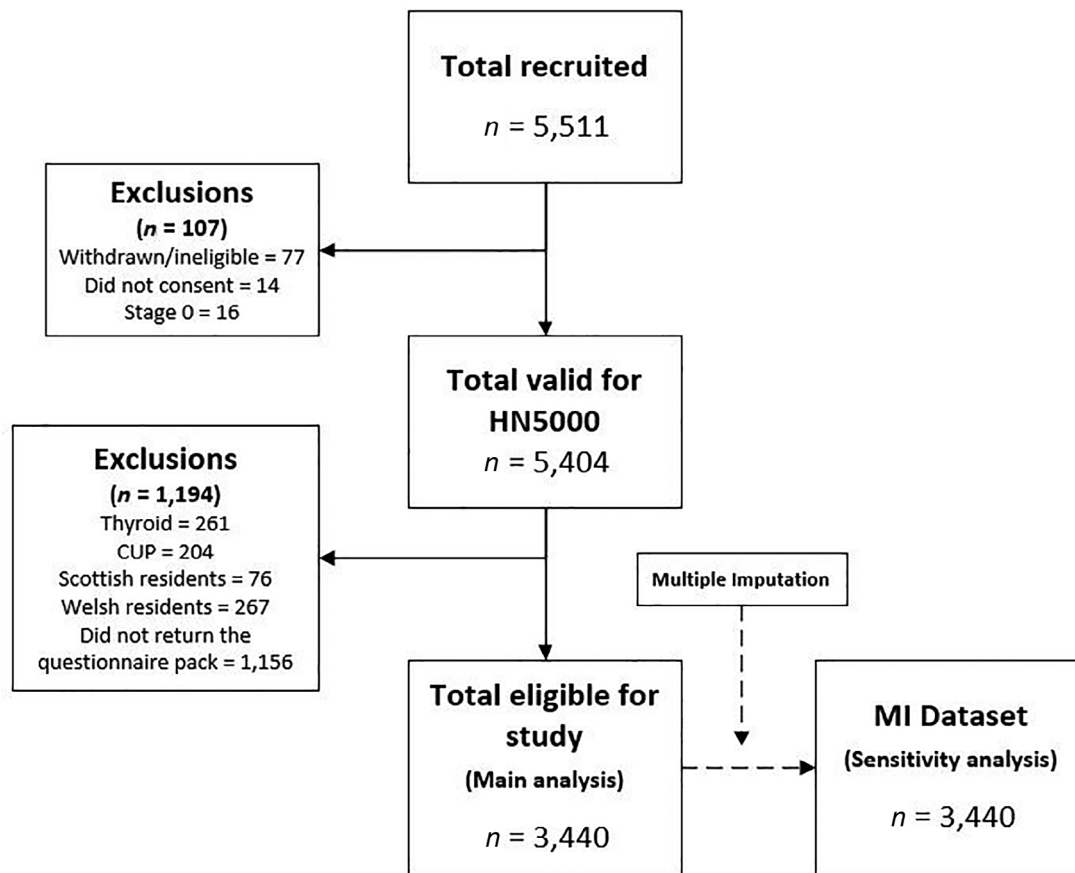


FIGURE 1 Flowchart of eligible cases included

2). Data were complete for age at date of consent, sex, anatomical site and treatment modality.

3.3 | Descriptive statistics

3.3.1 | Potential explanatory factors

The number of participants for each demographic, health, behavioral, tumor, and treatment factor are displayed in Table 1. Participants' age at date of consent ranged from 22 to 95 (median = 62 years). Nearly three quarters ($n = 2526/73.4\%$) of the cohort were male. More than a half ($n = 1881/54.7\%$) of the participants had at least a mild comorbidity; however, 52.3% ($n = 1799$) of the cohort were of normal WHO Performance Status. Approximately, three quarters ($n = 2527/73.5\%$) of the cohort were either current or former smokers, and 70.3% ($n = 2418$) of the participants were moderate to harmful drinkers. A proportion of 38.8% ($n = 1334$) people had tumors of the oropharynx, while 45.2% ($n = 1555$) tumors of the cohort had stage IV tumors, and 61.5% ($n = 2114$) of HPV negative tumors. Participants were more likely to be treated with chemoradiotherapy or a combination of surgery and chemoradiotherapy ($n = 1936/56.2\%$).

3.3.2 | SES factors

A number of participants for each of the SES factors are displayed in Table 2. There was an even spread of participants across the IMD Categories ranging from 17.9% ($n = 616$) to 21.7% ($n = 746$) (Table 2). Nearly half ($n = 1556/45.5\%$) of the cohort had attained an education level of up to secondary school, and nearly one third ($n = 1007/29.3\%$) of participants had spent 10 years or less in full-time education. More than half ($n = 1988/57.8\%$) of the cohort earned less than £29 000 per year, one third ($n = 1100/32.0\%$) of the cohort earned at least some of their income from benefits, and 34.3% ($n = 1181$) of people had financial concerns of living with or after cancer.

3.3.3 | Cross-tabulations of potential explanatory factors with SES factors

People in the most deprived IMD Category were more likely to be younger, have worse comorbidities, have worse WHO Performance Status, and be current smokers or harmful drinkers (Table S1). The most deprived group by IMD Category were also more likely to have tumors of

TABLE 1 Frequency, number of people who had died by October 2018, 3-year survival proportions, and age- and sex-adjusted Cox proportional hazard models for all demographic, health, behavioral, tumor, treatment, and SES factors

Variable	Frequency (col. %)	Died by October 2018 (row %)
Whole cohort	3440	1068 (31.1%)
Age group		
Less than 44	210 (6.1%)	37 (17.6%)
45 to 54	676 (19.7%)	156 (23.1%)
55 to 64	1192 (34.7%)	356 (29.9%)
65 to 74	940 (27.3%)	313 (33.3%)
75 and over	422 (12.3%)	206 (48.8%)
Sex		
Male	2526 (73.4%)	820 (32.5%)
Female	914 (26.6%)	248 (27.1%)
Marital status		
Single	427 (12.4%)	153 (35.8%)
Separated/divorced/widowed	686 (19.9%)	280 (40.8%)
Married/living with partner	2283 (66.4%)	620 (27.2%)
Unknown	44 (1.3%)	15 (34.1%)
Comorbidity		
No comorbidity	1484 (43.1%)	321 (21.6%)
Mild comorbidity	1149 (33.4%)	372 (32.4%)
Moderate/severe comorbidity	732 (21.3%)	352 (48.1%)
Unknown	75 (2.2%)	23 (30.7%)
WHO performance status		
Normal activity	1799 (52.3%)	377 (21.0%)
Strenuous activity restricted	843 (24.5%)	306 (36.3%)
Up and about >50%	470 (13.7%)	207 (44.0%)
Confined >50% or 100%	166 (4.8%)	105 (63.3%)
Unknown	162 (4.7%)	73 (45.1%)
Smoking status		
Current smoker	664 (19.3%)	301 (45.3%)
Former smoker	1863 (54.2%)	573 (30.8%)
Never smoked	740 (21.5%)	150 (20.3%)
Unknown	173 (5.0%)	44 (25.4%)
Alcohol consumption		
Non-drinker	911 (26.5%)	297 (32.6%)
Moderate	729 (21.2%)	179 (24.6%)
Hazardous	1210 (35.2%)	359 (29.7%)
Harmful	479 (13.9%)	182 (38.0%)
Unknown	111 (3.2%)	51 (46.0%)
Anatomical site		
Oropharynx	1334 (38.8%)	332 (24.9%)
Lip and oral cavity	900 (26.2%)	318 (35.3%)
Larynx	728 (21.2%)	214 (29.4%)

(Continues)

TABLE 1 (Continued)

Variable	Frequency (col. %)	Died by October 2018 (row %)
Hypopharynx	160 (4.7%)	96 (60.0%)
Salivary glands	147 (4.3%)	34 (23.1%)
Other	171 (5.0%)	74 (43.3%)
Stage		
I	788 (22.9%)	131 (16.6%)
II	593 (17.2%)	176 (29.7%)
III	473 (13.8%)	155 (32.8%)
IV	1555 (45.2%)	590 (37.9%)
Unknown	31 (0.9%)	16 (51.6%)
HPV status		
Negative	2114 (61.5%)	760 (36.0%)
Positive	867 (25.2%)	150 (17.3%)
Unknown	459 (13.3%)	158 (34.4%)
Treatment		
Surgery only	765 (22.2%)	167 (21.8%)
Chemoradiotherapy only	1064 (30.9%)	311 (29.2%)
Radiotherapy only	702 (20.4%)	255 (36.3%)
Surgery and chemo/radio	872 (25.3%)	302 (34.6%)
Chemotherapy only	15 (0.4%)	14 (93.3%)
No treatment	22 (0.6%)	19 (86.4%)
IMD category		
1—Most deprived	674 (19.6%)	257 (38.1%)
2	616 (17.9%)	188 (30.5%)
3	746 (21.7%)	227 (30.4%)
4	664 (19.3%)	186 (28.0%)
5—Least deprived	655 (19.0%)	182 (27.8%)
Unknown	85 (2.5%)	28 (32.9%)
Highest education level		
Up to secondary school	1556 (45.2%)	535 (34.4%)
Further education	827 (24.0%)	229 (27.7%)
Higher education/degree	849 (24.7%)	229 (27.0%)
Unknown	208 (6.0%)	75 (36.1%)
Time in education		
10 years or less	1007 (29.3%)	358 (35.6%)
11 to 13 years	1200 (34.9%)	334 (27.8%)
14 years or more	904 (26.3%)	263 (29.1%)
Unknown	329 (9.6%)	113 (34.4%)
Household income		
£11 999 or less	884 (25.7%)	344 (38.9%)
£12 000 to £28 999	1104 (32.1%)	336 (30.4%)
£29 000 or more	935 (27.2%)	187 (20.0%)
Unknown	517 (15.0%)	201 (38.9%)

TABLE 1 (Continued)

Variable	Frequency (col. %)	Died by October 2018 (row %)
Income from benefits		
All	487 (14.2%)	213 (43.7%)
Some	613 (17.8%)	231 (27.7%)
None	2126 (61.8%)	548 (25.8%)
Unknown	214 (6.2%)	76 (35.5%)
Financial concerns		
Yes	1181 (34.3%)	358 (30.3%)
No	2051 (59.6%)	631 (30.8%)
Unknown	208 (6.0%)	79 (38.0%)

the larynx, have tumors that were HPV negative, and be treated with radiotherapy only. People who had attained an education level of up to secondary school, spent less than 10 years in full-time education, earned £11 000 per annum or less, or earned all their income from benefits were more likely to have worse comorbidities, worse WHO Performance Status, be current smokers, have cancer of the larynx, and have HPV negative tumors (Tables S2–S5). Participants who had attained an education of up to secondary school or remained in full-time education for 10 years or less were also more likely to be older (Tables S2 and S3). Participants who earned £11 999 or less were also more likely to be female and have stage II tumors. In contrast, people who had specified that they had financial concerns of living with or after cancer were more likely to be younger and males with no comorbidities (Table S6).

3.4 | Overall survival

3.4.1 | Follow-up

The median follow-up time was 4.8 years (IQR = 4.3 to 5.6 years) and 1.6 years (IQR = 0.8 to 2.9 years) for those who were alive and had died by the end of the follow-up period, respectively.

3.4.2 | Survival for potential explanatory factors

Three-year overall survival and age- and sex-adjusted Cox Proportional Hazard models for all-cause mortality are displayed in Table 1 for all potential explanatory factors. Three-year survival for the whole cohort was 76.3% (95%

CI = 74.9% to 77.7%). People aged 75 and over had the lowest overall survival at 64.7% (95% CI = 59.9% to 69.0%) compared to those who were younger than 44 who had overall survival of 85.2% (95% CI = 79.7% to 89.4%). Males had lower overall survival than females at 75.5% (95% CI = 73.7% to 77.1%) and 78.8% (95% CI = 76.0% to 81.3%), respectively. Following the adjustment for age and sex, in both the models prior to and post MI, participants who were at the highest risk of all-cause mortality were not married or not living with a partner, had worse comorbidities, worse WHO Performance Status, were current or previous smokers, or were harmful drinkers. People were also more at risk of all-cause mortality following age and sex adjustment if they had tumors of the oral cavity, hypopharynx, or “other” head and neck sites, had tumors of higher stage, had HPV negative tumors or were treated with chemotherapy and/or radiotherapy (with or without surgery).

3.4.3 | Survival for SES factors

Three-year overall survival and age- and sex-adjusted Cox Proportional Hazard models for all-cause mortality prior to and post MI are displayed in Table 2 for all the SES factors. People had worse 3-year overall survival if they were of the most deprived IMD Category, attained an education of up to secondary school, or had remained in education for 10 years or less. People had lower 3-year survival if they earned less than £11 999 per household or earned all their income from benefits. Interestingly, there was no difference in 3-year survival by financial concerns of living with or after cancer. Following adjustment by age and sex, both prior to and post MI, participants remained at a higher risk of all-cause mortality if they resided in areas of the most deprived IMD Category (pre-

TABLE 2 Frequency, number of people who had died by October 2018, 3-year survival proportions, and age- and sex-adjusted Cox proportional hazard models for all demographic, health, behavioral, tumor, treatment, and SES factors

Variable	3-year survival		Age- and sex-adjusted prior to imputation		Age- and sex-adjusted after imputation	
	Percent (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Whole cohort	76.3 (74.9, 77.7)	-	a	a	a	a
Age group		<0.001				
Less than 44	85.2 (79.7, 89.4)		a	a	a	a
45 to 54	82.0 (78.8, 84.7)		a	a	a	a
55 to 64	77.8 (75.3, 80.0)		a	a	a	a
65 to 74	73.7 (70.8, 76.4)		a	a	a	a
75 and over	64.7 (59.9, 69.0)		a	a	a	a
Sex		0.006				
Male	75.5 (73.7, 77.1)		a	a	a	a
Female	78.8 (76.0, 81.3)		a	a	a	a
Marital status		<0.001				
Single	73.8 (69.3, 77.7)		1.58 (1.32, 1.89)	<0.001	1.58 (1.32, 1.90)	<0.001
Separated/divorced/widowed	67.8 (64.2, 71.1)		1.58 (1.37, 1.83)	<0.001	1.60 (1.38, 1.85)	<0.001
Married/living with partner	79.5 (77.7, 81.1)		1.00 (Ref.)	a	1.00 (Ref.)	a
Unknown	72.7 (57.0, 83.5)		1.35 (0.81, 2.26)	0.247	a	a
Comorbidity		<0.001				
No comorbidity	83.8 (81.9, 85.6)		1.00 (Ref.)	a	1.00 (Ref.)	a
Mild comorbidity	75.6 (73.0, 78.0)		1.45 (1.25, 1.70)	<0.001	1.45 (1.24, 1.69)	<0.001
Moderate/severe comorbidity	62.4 (58.8, 65.8)		2.32 (1.98, 2.71)	<0.001	2.29 (1.96, 2.68)	<0.001
Unknown	74.7 (63.2, 83.0)		1.43 (0.93, 2.18)	0.100	a	a
WHO performance status		<0.001				
Normal activity	84.1 (82.3, 85.7)		1.00 (Ref.)	a	1.00 (Ref.)	a
Strenuous activity restricted	72.2 (69.1, 75.1)		1.78 (1.53, 2.07)	<0.001	1.77 (1.52, 2.06)	<0.001
Up and about >50%	67.5 (63.0, 71.5)		2.30 (1.94, 2.73)	<0.001	2.31 (1.95, 2.74)	<0.001
Confined >50% or 100%	50.6 (42.8, 57.9)		3.95 (3.18, 4.91)	<0.001	3.84 (3.09, 4.79)	<0.001
Unknown	64.2 (56.3, 71.0)		2.28 (1.77, 2.94)	<0.001	a	a
Smoking status		<0.001				
Current smoker	65.5 (61.8, 69.0)		2.83 (2.32, 3.45)	<0.001	2.86 (2.34, 3.49)	<0.001
Former smoker	76.6 (74.6, 78.5)		1.56 (1.30, 1.87)	<0.001	1.56 (1.31, 1.87)	<0.001
Never smoked	84.6 (81.8, 87.0)		1.00 (Ref.)	a	1.00 (Ref.)	a
Unknown	79.8 (73.0, 85.0)		1.27 (0.91, 1.79)	0.157	a	a
Alcohol consumption		<0.001				
Non-drinker	75.9 (72.9, 78.5)		1.00 (Ref.)	a	1.00 (Ref.)	-
Moderate	81.5 (78.5, 84.1)		0.73 (0.61, 0.88)	0.001	0.75 (0.62, 0.90)	0.002
Hazardous	77.2 (74.7, 79.5)		0.92 (0.79, 1.08)	0.332	0.94 (0.80, 1.10)	0.430
Harmful	69.9 (65.6, 73.8)		1.41 (1.16, 1.70)	0.001	1.41 (1.17, 1.71)	<0.001
Unknown	64.9 (55.2, 72.9)		1.53 (1.13, 2.06)	0.005	a	a
Anatomical site		<0.001				
Oropharynx	81.7 (79.5, 83.7)		1.00 (Ref.)	a	b	b
Lip and oral cavity	71.4 (68.4, 74.3)		1.46 (1.24, 1.71)	<0.001	b	b

TABLE 2 (Continued)

Variable	3-year survival		Age- and sex-adjusted prior to imputation		Age- and sex-adjusted after imputation	
	Percent (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Larynx	79.1 (76.0, 81.9)		0.99 (0.82, 1.18)	0.871	^b	^b
Hypopharynx	48.1 (40.2, 55.6)		2.98 (2.37, 3.75)	<0.001	^b	^b
Salivary glands	85.0 (78.2, 89.9)		0.93 (0.65, 1.33)	0.677	^b	^b
Other	67.3 (59.6, 73.7)		1.98 (1.54, 2.55)	<0.001	^b	^b
Stage		<0.001				
I	89.1 (86.7, 91.1)		1.00 (Ref.)	^a	1.00 (Ref.)	-
II	78.9 (75.4, 82.0)		1.93 (1.54, 2.42)	<0.001	1.91 (1.53, 2.40)	<0.001
III	75.9 (71.8, 79.5)		2.35 (1.86, 2.97)	<0.001	2.33 (1.84, 2.94)	<0.001
IV	69.3 (67.0, 71.6)		3.01 (2.49, 3.64)	<0.001	2.97 (2.45, 3.59)	<0.001
Unknown	61.3 (42.0, 75.9)		4.01 (2.39, 6.74)	<0.001	^a	^a
HPV status		<0.001				
Negative	72.2 (70.2, 74.0)		1.00 (Ref.)	^a	1.00 (Ref.)	^a
Positive	88.1 (85.8, 90.1)		0.46 (0.38, 0.55)	<0.001	0.46 (0.39, 0.55)	<0.001
Unknown	73.2 (68.9, 77.0)		0.99 (0.84, 1.18)	0.933	^a	^a
Treatment		<0.001				
Surgery only	85.2 (82.5, 87.6)		1.00 (Ref.)	^a	^b	^b
Chemoradiotherapy only	77.1 (74.4, 79.5)		1.62 (1.34, 1.97)	<0.001	^b	^b
Radiotherapy only	73.2 (69.8, 76.3)		1.65 (1.35, 2.01)	<0.001	^b	^b
Surgery and chemo/radio	72.8 (69.7, 75.7)		1.85 (1.53, 2.24)	<0.001	^b	^b
Chemotherapy only	13.3 (2.2, 34.6)		11.69 (6.76, 20.22)	<0.001	^b	^b
No treatment	13.6 (3.4, 30.9)		17.57 (10.87, 28.39)	<0.001	^b	^b
IMD category		0.002				
1—Most deprived	71.2 (67.6, 74.5)		1.50 (1.24, 1.81)	<0.001	1.49 (1.23, 1.80)	<0.001
2	77.9 (74.4, 81.0)		1.13 (0.92, 1.38)	0.007	1.13 (0.92, 1.38)	0.240
3	77.8 (74.6, 80.6)		1.11 (0.91, 1.35)	0.129	1.11 (0.92, 1.35)	0.282
4	77.4 (74.0, 80.4)		0.98 (0.80, 1.20)	0.347	1.11 (0.92, 1.35)	0.816
5—Least deprived	77.3 (73.9, 80.3)		1.00 (Ref.)	^a	1.00 (Ref.)	^a
Unknown	77.7 (67.2, 85.1)		1.18 (0.79, 1.76)	0.291	^a	^a
Highest education level		<0.001				
Up to secondary school	74.2 (71.9, 76.3)		1.26 (1.08, 1.47)	0.003	1.26 (1.08, 1.47)	0.003
Further education	77.8 (74.8, 80.4)		1.07 (0.89, 1.29)	0.510	1.07 (0.89, 1.28)	0.496
Higher education/degree	79.4 (76.5, 82.0)		1.00 (Ref.)	^a	1.00 (Ref.)	^a
Unknown	74.5 (68.0, 79.9)		1.25 (0.96, 1.62)	0.099	^a	^a
Time in education		<0.001				
10 years or less	73.2 (70.3, 75.8)		1.10 (0.94, 1.29)	0.244	1.10 (0.94, 1.30)	0.229
11 to 13 years	78.9 (76.5, 81.1)		0.97 (0.82, 1.14)	0.676	0.98 (0.83, 1.15)	0.766
14 years or more	76.3 (73.4, 79.0)		1.00 (Ref.)	^a	1.00 (Ref.)	^a
Unknown	76.6 (71.6, 80.8)		1.19 (0.96, 1.49)	0.116	^a	^a
Household income		<0.001				
£11 999 or less	70.3 (67.1, 73.1)		2.00 (1.67, 2.40)	<0.001	1.92 (1.61, 2.28)	<0.001
£12 000 to £28 999	77.6 (75.0, 79.9)		1.47 (1.22, 1.76)	<0.001	1.43 (1.20, 1.70)	<0.001

(Continues)

TABLE 2 (Continued)

Variable	3-year survival		Age- and sex-adjusted prior to imputation		Age- and sex-adjusted after imputation	
	Percent (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
£29 000 or more	83.7 (81.2, 86.0)		1.00 (Ref.)	^a	1.00 (Ref.)	^a
Unknown	70.8 (66.7, 74.5)		1.87 (1.52, 2.30)	<0.001	^a	^a
Income from benefits		<0.001				
All	68.4 (64.1, 72.3)		1.93 (1.64, 2.26)	<0.001	1.91 (1.63, 2.25)	<0.001
Some	71.8 (68.0, 75.2)		1.47 (1.26, 1.71)	<0.001	1.45 (1.25, 1.69)	<0.001
None	79.9 (78.2, 81.6)		1.00 (Ref.)	^a	1.00 (Ref.)	^a
Unknown	72.0 (65.4, 77.5)		1.24 (0.97, 1.58)	0.088	^a	^a
Financial concerns		0.102				
Yes	76.5 (73.9, 78.8)		1.19 (1.04, 1.37)	0.013	0.83 (0.73, 0.96)	0.011
No	76.7 (74.9, 78.5)		1.00 (Ref.)	^a	1.00 (Ref.)	^a
Unknown	71.6 (65.0, 77.3)		1.13 (0.89, 1.44)	0.301	^a	^a

^aNot applicable.^bNot imputed since data were complete so results would be the same as non-imputed model.

MI HR = 1.50, 95% CI = 1.24 to 1.81; post-MI HR = 1.49, 95% CI = 1.23 to 1.80), or attained an education level of up to secondary school (pre-MI HR = 1.26, 95% CI = 1.08 to 1.47; post-MI HR = 1.26, 95% CI = 1.08 to 1.47). In addition, participants were also more at risk of all-cause mortality after age and sex adjustment if they earned less than £11 999 per annum (pre-MI HR = 2.00, 95% CI = 1.67 to 2.40; post-MI HR = 1.92, 95% CI = 1.61 to 2.28), or earned all their income from benefits (pre-MI HR = 1.93, 95% CI = 1.64 to 2.26; post-MI HR = 1.91, 95% CI 1.63 to 2.25). Prior to MI, there was a difference between participants with financial concerns of living with or after cancer following age and sex adjustment (HR = 1.19, 95% CI = 1.04 to 1.37); however, following MI, the difference between the people with and without financial concerns following age and sex adjustment was reversed (HR = 0.83, 95% CI = 0.73 to 0.96). Following age and sex adjustment, there was no longer a difference in all-cause mortality for the participants who had spent less time in full-time education, which would be expected given the higher proportion of older people who had remained in education for less time.

3.5 | Explanations for inequality in survival

Adjusted Cox Proportional Hazard Models for all-cause mortality to determine the explanations for inequality in the survival of people with HNC are displayed in Table 3 prior to imputation and Table 4 following imputation.

3.5.1 | IMD category

Prior to MI, following adjustment by age, sex and a) comorbidity; b) smoking status; c) alcohol consumption; or d) tumor and treatment factors combined, there was an attenuation in inequality by IMD Category (particularly by smoking status adjustment) but inequality by IMD Category remained strong. When the model was adjusted by age, sex and all health and behavioral factors including comorbidity, smoking status and alcohol consumption, there was no longer an inequality in all-cause mortality by IMD Category (Most deprived HR = 1.07, 95% CI = 0.88 to 1.31). Following MI, results were comparable to those of the models prior to MI for IMD Category.

3.5.2 | Highest education level attained

Following adjustment by age, sex, and (a) comorbidity; or (b) alcohol consumption, there was a slight attenuation in inequality by highest education level attained but the inequality remained strong. When the model was adjusted by age, sex and smoking status, participants who attained an education level up to secondary school were no longer at a higher risk of all-cause mortality (HR = 1.13, 95% CI 0.95 to 1.32) than those who continued to higher education or degree. Similar results were also observed when the model was adjusted by all tumor and treatment factors combined (HR = 1.13, 95% CI 0.97 to 1.33) but no tumor or treatment factor attenuated

TABLE 3 Cox proportion hazards models for each SES factors prior to imputation

	Age, sex, and comorbidity adjusted			Age, sex, and smoking adjusted			Age, sex, and alcohol adjusted			Age, sex, health, and behavioral factors adjusted ^a			Age, sex, tumor, and treatment factors adjusted ^b			Fully adjusted ^c		
	HR (95% CI)	p-value		HR (95% CI)	p-value		HR (95% CI)	p-value		HR (95% CI)	p-value		HR (95% CI)	p-value		HR (95% CI)	p-value	
IMD category																		
1—Most deprived	1.32 (1.09, 1.60)	0.005		1.22 (1.00, 1.48)	0.046		1.40 (1.16, 1.70)	0.001		1.07 (0.88, 1.31)	0.480		1.37 (1.13, 1.66)	0.001		1.08 (0.88, 1.31)	0.473	
2	1.06 (0.86, 1.30)	0.596		1.00 (0.81, 1.23)	0.991		1.09 (0.89, 1.34)	0.392		0.94 (0.76, 1.15)	0.550		1.10 (0.89, 1.35)	0.380		0.95 (0.77, 1.16)	0.597	
3	1.05 (0.87, 1.28)	0.598		1.04 (0.85, 1.26)	0.710		1.08 (0.89, 1.32)	0.431		0.98 (0.81, 1.08)	0.872		1.07 (0.88, 1.30)	0.510		0.97 (0.79, 1.18)	0.744	
4	0.94 (0.77, 1.16)	0.577		0.93 (0.75, 1.14)	0.464		0.95 (0.77, 1.17)	0.629		0.88 (0.72, 1.08)	0.218		0.93 (0.76, 1.15)	0.519		0.84 (0.68, 1.03)	0.101	
5—Least deprived	1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d	
Unknown	1.08 (0.73, 1.61)	0.699		1.03 (0.69, 1.54)	0.874		1.09 (0.73, 1.62)	0.686		0.92 (0.62, 1.38)	0.688		0.95 (0.64, 1.43)	0.817		0.72 (0.48, 1.09)	0.120	
Highest education																		
Up to secondary	1.20 (1.03, 1.40)	0.019		1.13 (0.96, 1.32)	0.123		1.24 (1.06, 1.45)	0.005		1.09 (0.93, 1.27)	0.265		1.13 (0.97, 1.33)	0.109		1.00 (0.86, 1.18)	0.882	
Further education	1.04 (0.86, 1.25)	0.741		1.04 (0.87, 1.25)	0.680		1.07 (0.89, 1.28)	0.540		1.02 (0.85, 1.22)	0.875		1.05 (0.88, 1.26)	0.584		1.00 (0.84, 1.21)	0.893	
Higher/degree	1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d	
Unknown	1.19 (0.92, 1.55)	0.182		1.14 (0.88, 1.49)	0.331		1.18 (0.90, 1.53)	0.224		1.07 (0.82, 1.40)	0.616		1.18 (0.91, 1.54)	0.208		1.04 (0.79, 1.36)	0.788	
Time in education																		
10 years or less	1.05 (0.90, 1.24)	0.519		1.06 (0.90, 1.24)	0.500		1.10 (0.94, 1.29)	0.248		1.03 (0.87, 1.20)	0.757		1.05 (0.89, 1.23)	0.574		0.99 (0.84, 1.17)	0.895	
11 to 13 years	0.94 (0.80, 1.11)	0.489		0.97 (0.82, 1.14)	0.682		0.97 (0.83, 1.14)	0.719		0.95 (0.81, 1.12)	0.528		1.02 (0.87, 1.20)	0.802		1.02 (0.86, 1.20)	0.835	
14 years or more	1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d		1.00 (Ref.)	^d	
Unknown		0.142			0.149			0.181			0.236			0.087			0.173	

(Continues)

TABLE 3 (Continued)

	Age, sex, and comorbidity adjusted		Age, sex, and smoking adjusted		Age, sex, and alcohol adjusted		Age, sex, health, and behavioral factors adjusted ^a		Age, sex, tumor, and treatment factors adjusted ^b		Fully adjusted ^c	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Annual income	1.18 (0.95, 1.47)		1.18 (0.94, 1.48)		1.16 (0.93, 1.45)		1.15 (0.92, 1.43)		1.21 (0.97, 1.52)		1.17 (0.93, 1.47)	
	1.76 (1.47, 2.12)	<0.001	1.64 (1.36, 1.97)	<0.001	1.92 (1.60, 2.31)	<0.001	1.46 (1.21, 1.76)	<0.001	1.67 (1.39, 2.01)	<0.001	1.34 (1.01, 1.63)	0.003
	1.39 (1.16, 1.66)	<0.001	1.32 (1.10, 1.58)	0.003	1.45 (1.21, 1.74)	<0.001	1.26 (1.05, 1.52)	0.012	1.33 (1.10, 1.59)	0.002	1.17 (0.97, 1.41)	0.100
	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d
	1.71 (1.39, 2.10)	<0.001	1.64 (1.33, 2.02)	<0.001	1.77 (1.43, 2.18)	<0.001	1.46 (1.18, 1.80)	0.001	1.48 (1.20, 1.83)	<0.001	1.25 (1.00, 1.55)	0.047
Income benefits	1.63 (1.39, 1.92)	<0.001	1.61 (1.37, 1.89)	<0.001	1.82 (1.55, 2.13)	<0.001	1.36 (1.15, 1.60)	<0.001	1.69 (1.44, 1.99)	<0.001	1.35 (1.14, 1.60)	0.001
	1.34 (1.14, 1.57)	<0.001	1.39 (1.19, 1.63)	<0.001	1.45 (1.24, 1.69)	<0.001	1.27 (1.08, 1.49)	0.003	1.40 (1.19, 1.63)	<0.001	1.27 (1.09, 1.49)	0.003
	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d
	1.13 (0.88, 1.44)	0.336	1.16 (0.91, 1.48)	0.242	1.17 (0.92, 1.51)	0.194	1.03 (0.81, 1.33)	0.788	1.09 (0.85, 1.40)	0.483	0.96 (0.75, 1.24)	0.768
Financial concerns	1.14 (0.99, 1.31)	0.062	1.12 (0.97, 1.28)	0.127	1.17 (1.02, 1.35)	0.024	1.07 (0.93, 1.24)	0.319	1.01 (0.88, 1.17)	0.847	0.94 (0.81, 1.08)	0.371
	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d
	1.10 (0.87, 1.40)	0.424	1.08 (0.85, 1.37)	0.523	1.06 (0.83, 1.35)	0.626	1.01 (0.79, 1.29)	0.936	0.96 (0.75, 1.22)	0.716	0.90 (0.71, 1.16)	0.424

^aAdjusted by age, sex, comorbidity, smoking, and alcohol.^bAdjusted by age, sex, anatomical site, TNM stage, HPV status, and treatment modality.^cAdjusted by age, sex, comorbidity, smoking, alcohol, anatomical site, TNM stage, HPV status, and treatment modality.^dNot applicable.

TABLE 4 Cox proportion hazards models for each SES factors for the imputed datasets

	Age, sex, and comorbidity adjusted		Age, sex, and smoking adjusted		Age, sex, and alcohol adjusted		Age, sex, health, and behavioral factors adjusted ^a		Age, sex, tumor, and treatment factors adjusted ^b		Fully adjusted ^c	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
IMD category												
1—Most deprived	1.32 (1.09, 1.60)	0.005	1.20 (0.99, 1.46)	0.066	1.42 (1.17, 1.72)	<0.001	1.08 (0.89, 1.31)	0.453	1.34 (1.10, 1.62)	0.003	1.06 (0.87, 1.30)	0.565
2	1.06 (0.87, 1.30)	0.563	0.99 (0.81, 1.22)	0.938	1.10 (0.89, 1.34)	0.376	0.94 (0.76, 1.15)	0.539	1.08 (0.88, 1.33)	0.472	0.93 (0.75, 1.14)	0.478
3	1.06 (0.87, 1.29)	0.554	1.03 (0.85, 1.26)	0.746	1.09 (0.90, 1.32)	0.383	0.99 (0.81, 1.20)	0.915	1.06 (0.87, 1.30)	0.550	0.97 (0.79, 1.18)	0.731
4	0.94 (0.77, 1.16)	0.581	0.92 (0.75, 1.13)	0.442	0.95 (0.78, 1.17)	0.654	0.89 (0.72, 1.09)	0.245	0.92 (0.75, 1.13)	0.452	0.84 (0.69, 1.04)	0.104
5—Least deprived	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d
Highest education												
Up to secondary	1.21 (1.03, 1.41)	0.018	1.12 (0.96, 1.31)	0.151	1.26 (1.08, 1.47)	0.004	1.09 (0.93, 1.27)	0.292	1.14 (0.98, 1.34)	0.082	1.02 (0.87, 1.20)	0.799
Further education	1.03 (0.86, 1.24)	0.711	1.03 (0.86, 1.24)	0.712	1.06 (0.89, 1.27)	0.509	1.01 (0.84, 1.21)	0.899	1.04 (0.87, 1.25)	0.658	1.00 (0.83, 1.21)	0.971
Higher/degree	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d
Time in education												
10 years or less	1.06 (0.90, 1.24)	0.486	1.05 (0.90, 1.23)	0.534	1.11 (0.94, 1.30)	0.216	1.02 (0.87, 1.20)	0.768	1.05 (0.89, 1.24)	0.541	0.99 (0.84, 1.17)	0.951
11 to 13 years	0.96 (0.81, 1.12)	0.582	0.97 (0.83, 1.14)	0.727	0.98 (0.83, 1.16)	0.834	0.96 (0.81, 1.13)	0.594	1.02 (0.86, 1.20)	0.852	1.01 (0.86, 1.19)	0.895
14 years or more	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d	1.00 (Ref.)	^d
Annual income												
£11 999 or less	1.71 (1.43, 2.04)	<0.001	1.57 (1.31, 1.87)	<0.001	1.86 (1.56, 2.22)	<0.001	1.42 (1.18, 1.70)	<0.001	1.61 (1.34, 1.94)	<0.001	1.32 (1.09, 1.59)	0.004
£12 000 to £28 999	1.35 (1.14, 1.61)	0.001	1.29 (1.08, 1.53)	0.004	1.41 (1.19, 1.68)	<0.001	1.23 (1.04, 1.47)	0.019	1.29 (1.08, 1.54)	0.005	1.15 (0.96, 1.37)	0.123

(Continues)

TABLE 4 (Continued)

	Age, sex, and comorbidity adjusted			Age, sex, and smoking adjusted			Age, sex, and alcohol adjusted			Age, sex, health, and behavioral factors adjusted ^a			Age, sex, tumor, and treatment factors adjusted ^b			Fully adjusted ^c		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value	HR	(95% CI)	p-value	HR	(95% CI)	p-value	HR	(95% CI)	p-value	HR	(95% CI)	p-value
£29 000 or more	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d
Income benefits																		
All	1.63 (1.38, 1.93)		<0.001	1.60 (1.36, 1.89)		<0.001	1.85 (1.57, 1.18)		<0.001	1.38 (1.16, 1.64)		<0.001	1.67 (1.42, 1.97)		<0.001	1.36 (1.14, 1.62)		<0.001
Some	1.33 (1.14, 1.55)		<0.001	1.37 (1.18, 1.60)		<0.001	1.44 (1.24, 1.68)		<0.001	1.26 (1.08, 1.47)		0.004	1.37 (1.18, 1.61)		<0.001	1.25 (1.07, 1.46)		0.005
None	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d
Financial concerns																		
Yes	0.87 (0.76, 1.00)		0.053	0.90 (0.78, 1.03)		0.125	0.85 (0.74, 0.98)		0.021	0.93 (0.81, 1.07)		0.295	0.97 (0.84, 1.12)		0.699	1.04 (0.91, 1.20)		0.541
No	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d	1.00 (Ref.)		^d

^aAdjusted by age, sex, comorbidity, smoking, and alcohol.
^bAdjusted by age, sex, anatomical site, TNM stage, HPV status, and treatment modality.
^cAdjusted by age, sex, comorbidity, smoking, alcohol, anatomical site, TNM stage, HPV status, and treatment modality.
^dNot applicable.

inequality by highest education level attained (data not shown). Following MI, the results were comparable to those prior to MI.

3.5.3 | Annual household income

Following adjustment by age, sex, and (a) comorbidity; (b) smoking status; (c) alcohol consumption; (d) health and behavioral factors; (e) tumor and treatment factors; or (f) all potential explanatory factors, there was a slight attenuation in inequality by annual household income (particularly by smoking status or all health and behavioral factors); however, the inequality remained strong. After full adjustment, the inequality by annual household income attenuated; however, people who earned less than £11 999 remained 34% (HR = 1.34, 95% CI = 1.01 to 1.63) more at risk of all-cause mortality than those who earned more than £29 000. The results from the imputed models were comparable to those prior to imputation.

3.5.4 | Income from benefits

Following adjustment by age, sex, and (a) comorbidity; (b) smoking status; (c) alcohol consumption; (d) health and behavioral factors; (e) tumor and treatment factors; or (f) all potential explanatory factors, there was attenuation in inequality by the proportion of income participants received from benefits; however, the inequality remained strong. After full adjustment, the inequality by proportion of income from benefits attenuated; however, the participants who earned all their income from benefits remained 35% (HR = 1.35, 95% CI = 1.14 to 1.60) more at risk of all-cause mortality than those who earned none of their income from benefits. Following MI, results were comparable to those prior to MI.

3.5.5 | Financial concerns

Following adjustment by age, sex, and (a) comorbidity; or (b) alcohol consumption, the inequality by financial concerns attenuated; however, it remained clear. When the model was adjusted by age, sex, and smoking status, participants who had financial concerns were no longer at a higher risk of all-cause mortality (HR = 1.12, 95% CI = 0.97 to 1.28). Similar results were also observed when the model was adjusted by age, sex, and (a) health and behavioral factors (HR = 1.07, 95% CI = 0.93 to 1.24), or (b) tumor and treatment factors combined (HR = 1.01, 95% CI = 0.88 to 1.17), but no tumor or treatment factor attenuated the inequality by financial

concerns (data not shown). Following MI, results were comparable to those prior to MI.

4 | DISCUSSION

Inequality in the survival of people with HNC was observed for several measurements of SES including IMD Category, highest education level, number of years spent in education, annual household income, proportion of income from benefits and financial concerns of living with or after cancer. Participant smoking status had a strong effect on inequality by IMD Category; however, adjustment for age, sex, health, and behavioral factors fully explained inequality by IMD Category. Similar results were observed for highest education attained and financial concerns; however, adjustment by smoking status fully explained the inequality by these factors alone, before and after MI. Inequality by annual household income and proportion of income from benefits attenuated following adjustment of all potential explanatory factors; however, even after full adjustment, inequalities remained strong before and after MI.

Previous work investigated the inequality in long-term survival as part of the Scottish Audit of Head and Neck Cancer (SAHNC)—a clinical cohort study of people with HNC in Scotland diagnosed between 1999 and 2001.¹³ A gradient in overall, disease-specific and net survival was observed at one-, five- and 12-years, and inequality by all-cause and disease-specific mortality was no longer evident following adjustment of combined patient, tumor and treatment factors. However, the SAHNC study investigated people with HNC from Scotland diagnosed approximately 15 years before the HN5000 study, from which we only included patients from England. Survival has differed between both countries for many years,³⁸ suggesting that people in England have a longer life expectancy than those in Scotland. In contrast to HN5000, the SAHNC study investigated survival using the area-based Carstairs 2001 Index^{39,40} which derives deprivation through low social class, lack of car ownership, overcrowding and male unemployment, and therefore cannot be compared to English IMD Categories. In addition, due to the long follow-up period, one limitation of the SAHNC study was that it was recruited ahead of the discovery of the association between HPV positivity and improved prognosis,^{41–43} and as a result, HPV was not available in the SAHNC study. Moreover, the SAHNC study did not have the advantage of the use of individual measurements of SES.

Other UK-based studies have investigated the impact of SES on survival of people with HNC, and inequality was explained by people with lower SES status having

tumors of higher stage, worse comorbidities, or poorer access to health care.^{10,11,44} In our study, inequality was not explained by these factors alone, particularly for annual household income and the proportion of income the participants received from benefits. However, it was clear that comorbidity attenuated inequalities by each SES factors, but inequality was not fully explained by comorbidity. Interestingly, inequality by IMD category and highest education level received considerably attenuated following the adjustment for smoking status. In this study, it was not clear that adjustment by tumor stage alone had any influence on survival for any of the SES factors (data not shown).

There are several limitations to this study. Firstly, the proportion of participants across the IMD groups was even, suggesting an under-representation of the most deprived people in this study.⁴⁵ As a result, this study may underestimate the true extent of inequality in survival of people with HNC. Secondly, participants were given the option of taking home their baseline questionnaire to complete and return with a pre-paid envelope. We compared those who did and did not return their questionnaires and discovered non-returns were more likely to be from more deprived IMD Categories (Table S8). Previous studies have also implied that non-respondents tend to be from backgrounds of lower SES and have less time and capacity to participate in research.^{46,47} Thirdly, after excluding a proportion of people who did not return their questionnaire, those with missing data for alcohol consumption and stage were at a higher risk of all-cause mortality compared to the healthier groups of individuals. However, we performed MI to overcome this issue. Finally, although we linked these data to mortality data, we were unable to obtain information on the cause of the participants' death. Therefore, we were only able to investigate the inequality in survival using all-cause mortality. However, due to the short-term follow-up period of this study, it is likely that a high proportion of deaths would be attributed to HNC, and therefore all-cause and disease-specific mortality results would be unlikely to be substantially different.⁴⁸

This study has several strengths. Firstly, the data are from a large, prospective, clinical cohort study which provided a range of measurements of SES including area-based and individual measurements. Due to the amount of data collected via medical records and participant questionnaires, this study allowed investigation into many potential explanatory factors of inequality in the survival of people with HNC via a wide range of factors including participant characteristics, demographics, behavioral, health, tumor and treatment factors.

We show that inequality by an area-based measurement of IMD Category could be mostly explained by

smoking status, and fully explained by a combination of age, sex, health and behavioral factors. Highest education level attained by the study population could also be mostly explained by smoking status, and fully explained by a combination of age, sex, health, and behavioral factors. Full adjustment attenuated inequality by annual household income and proportion of income from benefits; however, we were unable to fully explain inequality by these individual measurements of SES. This study adds to the literature by exploring inequalities in the survival of people with HNC using both area-based and individual measurements of SES, and by investigating the explanations for the inequalities observed. To our knowledge, this is the first study to investigate survival inequalities of people with HNC in such depth using both area-based and individual measurements and exploring the origins and explanations for the inequalities observed.

5 | CONCLUSIONS

Our findings that inequalities in both household income and the proportion of income from benefits are independently associated with HNC survival support that interventions that address these issues (e.g., income maximization and welfare benefit support) are included within the wider care provided to people with HNC.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Head and Neck 5000. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors at <http://www.headandneck5000.org.uk> with the permission of Head and Neck 5000.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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